NECROSIS OF THE BONE MARROW WITH FAT EMBOLISM IN SICKLE CELL ANEMIA*

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INTRODUCTION

Fat embolism has been described in a wide variety of clinical conditions. The importance of this complication in instances of trauma to bone or fatty tissues is well recognized. Few have agreed, however, that the finding of fat emboli in other conditions is of any practical importance.

A number of investigators have shown that the examination of routine necropsy material for fat embolism will reveal positive findings in a certain proportion of the cases. Lehman and McNattin [1] found varying degrees of fat embolism in the lungs in 37 of 50 autopsies. The embolism was described as moderate to marked in 13 instances, 6 of which were unassociated with trauma. More recently, Vance,[2] in a study of 246 necropsies, found "very slight fat embolism" in only 7 of the 82 cases which were unassociated with trauma. His conclusions were in accordance with the much earlier observations of Warthin,[3] who stated that in nontraumatic cases "the fat is so small in amount and the lesions so few, as to be of pathologic interest only."

We have recently had opportunity to study a case of sickle cell anemia in which the clinical picture and the pathological findings leave no doubt that fat embolism was an important factor in bringing about the patient's death. Groskloss [4] and Warthin [3] stated that fat embolism occurs in certain anemias. We have been unable, however, to find any report of a case similar to ours.

REPORT OF CASE

Clinical History. (N. Y. H. No. 59202.) The patient was a Greek housewife, 49 years old, who was admitted to the New York Hospital on four occasions.

Family History. The available family history was meager, but both of the patient's parents were said to be dead of causes unknown. They were born

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in Greece, of Greek parentage. There was no known history of familial disease.

Past History. The patient's general health was said to have been good, except for "nervousness," until March 1934, when she was admitted to the Surgical Service. She had been awakened from her sleep by a severe pain said to have been present throughout her entire body, but most severe in the right upper quadrant of the abdomen. The onset of the pain was associated with vomiting; attempts to drink water or to take food were followed by further vomiting. The pain was constant in nature and unrelieved by heat. The patient's husband stated that she had had a similar attack 3 years before, but none before or after to his knowledge. The only positive physical findings were: anemia, slight icterus, slight spasm and definite tenderness in the right upper quadrant.

A tentative diagnosis of acute cholecystitis was made and a laparotomy was performed. No stones were present and the gallbladder was not inflamed. No lesion was found to explain the patient's symptoms. The patient received four transfusions with a total of 1450 cc. of blood. She was discharged on April 15, 1934.

The patient was brought to the Emergency Pavilion on June 9, 1934, complaining of pains "like pins and needles" over the entire body. The patient was highly excitable but the physical examination was otherwise negative. She was given phenobarbital and sent home.

The patient was admitted to the Gynecological Service on January 22, 1935 because of metrorrhagia. Dilatation and curettage were done. The endometrial tissue removed was that of a postmenopausal uterus.

On October 5, 1935 the patient was again seen in the Emergency Pavilion. She complained of severe pain "just like last time," associated with nausea and vomiting. The patient was moaning, screaming, and lashing about in bed. She was admitted to the Surgical Service where she was observed for 24 hours. The pain subsided and in view of an entirely negative physical examination the patient was discharged.

The patient got along well until 1939. In that year she had several episodes of pain, nausea and vomiting, associated with "darkening of the skin."

Present Illness. At 2 a.m. on January 1, 1940 the patient was awakened from her sleep and caused to cry out by excruciating pain in the lumbar region of the spine. The pain returned in paroxysms and became generalized. The paroxysms of pain caused the patient to "break out in cold sweat." The pain was associated with vomiting and the patient continued to vomit all ingested food or water up to the time of admission to the Medical Service on January 4. On the day before admission the patient had severe shaking chills; her temperature rose to 102° F. and she became comatose.

Physical Examination. Temperature 39° C. Pulse 122. Respirations 38. Blood pressure 132/64. The patient was obviously critically ill. She was semicomatose. The neck was slightly stiff. There were petechiae in the conjunctivae and skin. The spleen was palpable. The liver was slightly enlarged. There was questionable icterus.

Laboratory Findings. These are summarized in Table I.

Course and Treatment. Throughout the patient's hospital stay her temperature varied from 38.6° to 40° C. The patient was at all times semistuporous. She was given six blood transfusions, totalling 2250 cc. of

TABLE I
Laboratory Findings in Case Reported

	Admission												
	I (1934)					II (1935)	III (1935)	IV (1940)					
Date	3/19	3/23	3/24	3/26	3/29	1/22	10/5	1/4	1/6	1/8	1/9	1/12	1/13
R. b. c. (millions per cu. mm.)	2.7	1.9	2.4	3.2	3.6			2.3	3.1	3.7	3.4	3.5	3.6
Hb. (14.5 gm. per 100 cc. = 100%)	55%	38%	48%	60%	70%	74%	85%	41%	50%	60%	60%	60%	66%
Cell volume						33%		15%			23%		
Sickle cells			+	+	—				—				
Reticulocytes									4.2				
Anisocytosis			+	+				+	+	+	+	+	+
Poikilocytosis			+	+				+	+	+	+	+	+
Nucleated r. b. c. (% of w. b. c.)			50%	67%				6%		35%	31%	22%	15%
W. b. c. (corrected)	8950	23,300	23,000	20,000	11,800	3250	7200	11,700	12,000	8500	7100	6500	7600
Adult polys	26%			23%				50%	60%	57%	55%	34%	21%
Immature polys	52%			56%				15%	18%	9%	11%	43%	47%
Lymphocytes	15%			11%				29%	20%	23%	27%	22%	30%
Platelets				260,000									
Bleeding time*				3 min.					3.5 min.				
Clotting time**				4 min.					9 min.				
Fragility					Normal				Normal				
Sedimentation rate†						0.1		0.05			0.1		
Icteric index	19	36	25	23	19			15		9			

* Duke method: Normal = 1 to 3 minutes
** Lee and White: Normal = 5 to 10 minutes
† Rourke and Ernstene: Normal = 0.08 to 0.35 mm. per minute

citrated blood. She was unable to take food by mouth and was given repeated infusions of 5 per cent glucose in saline solution. The petechiae noted on admission gradually faded and no new ones appeared. Her neck remained stiff but no Kernig or Babinski signs were elicited. The spinal fluid pressure was 140 mm. of water, the fluid was clear and there were three lymphocytes per cu. mm. Cultures of the fluid were sterile. The protein was 40 mg. per cent; sugar 92 mg. per cent; chlorides 740 mg. per cent; and the Wassermann negative. The patient's condition remained unchanged until the tenth hospital day, when she became more deeply comatose and her respirations became rapid and shallow. The blood pressure fell to 90/60. She became deeply cyanotic. The patient was placed in an oxygen tent and given respiratory stimulants but these were of no avail and the patient expired a few hours later.

Postmortem Examination

The description will be confined to the positive findings.

Macroscopic Examination. The *spleen* weighed 350 gm. It was adherent to the adjoining structures but was easily separated. The capsule was pale green in color and slightly wrinkled. On the surface were many gray areas with irregular "map-like" boundaries. These varied from a few millimeters to 2 cm. in diameter. The spleen was moderately firm but definitely "lumpy" in consistency. The "lumpy" areas of increased density corresponded to the gray areas described above. The spleen cut with a gritting sensation. The cut surface was dark red in color except for gray areas similar to those described on the surface. These occupied approximately 25 per cent of the cut surface. The *liver* weighed 1610 gm. Many pale, roughly circular areas, less than 1 mm. in diameter, were apparent on the cut surface of the liver. The *kidneys* each weighed 160 gm. The glomeruli stood out prominently as tiny hemorrhagic spots on the capsular and cut surfaces. The *bone marrow* was pale in color. The *arachnoid* of the interpeduncular space was slightly thickened. There was widespread cortical atrophy of the *brain.*

Microscopic Examination. The capsule and trabeculae of the *spleen* were moderately thickened by collagen fibers, between which were clusters of golden brown refractile bodies, roughly cylindrical in outline and in many instances segmented so as to resemble "bamboo poles." These bodies were made up chiefly of iron pigment. Similar masses of iron pigment and collagen fibers were present throughout the pulp. Such nodules were surrounded by dilated sinusoids containing many sickle cells and macro-

phages. The macrophages were loaded with erythrocytes and iron pigment. All of the malpighian corpuscles appeared to be involved. There were pale-staining areas of necrosis scattered irregularly through the pulp. The blood vessels were surrounded by collagen fibers and iron pigment but no thrombi were found.

The sinusoids of the *liver* were congested. The adjacent liver cells were extensively vacuolated and contained an unusually large amount of bile pigment. There were many bile thrombi in the biliary canaliculi. Small focal areas of necrosis of liver cells were present.

Material obtained by aspiration biopsy of the *sternal marrow* before death was necrotic and could not be stained satisfactorily. Sections prepared from postmortem material were also characterized by widespread necrosis with marked reduction in the blood-forming constituents and fat. The necrotic areas consisted of a faintly eosinophilic network in which were scattered granular debris, occasional polymorphonuclear leukocytes and numerous macrophages loaded with fat and chromatin particles. Foci of erythrogenesis contained mature cells, many of which were sickle shaped. Myelogenesis was normal. The megakaryocytes were reduced in number.

In the *brain* were many small areas of focal necrosis, both in the gray matter and in the white matter (Fig. 1). In the middle of some of these foci a few red blood cells were present. In addition there were many small hemorrhages, both in the cerebral cortex and in the cerebellum. These hemorrhages were usually perivascular. In these areas many of the red blood cells showed extreme degrees of sickling (Fig. 2). Wherever hemorrhage had occurred there was considerable proliferation of microglia cells although none had yet attained the form of gitter cells. Associated with this was a definite increase in the number of astrocytes in these areas. There were many fat emboli throughout the brain and in many instances the small areas of focal necrosis showed a capillary, either in the center of the area or just to one side, filled with droplets of fat (Fig. 3).

Frozen sections of lung, liver, kidney and spleen stained for fat contained many droplets in the arterioles and capillaries (Figs. 4 and 5).

Anatomical Diagnosis. Sickle cell anemia; splenomegaly (350

gm.) with areas of necrosis and siderofibrotic nodules; icterus; bile pigment thrombi in biliary canaliculi; focal necrosis of the bone marrow; fat emboli in lungs, brain, liver, spleen and kidneys; disseminated focal necrosis of the brain due to fat emboli.

Discussion

Sickle cell anemia is rare in the white race and it is quite unusual for patients more than 30 years of age to present clinical evidences of this disease. The diagnosis of sickle cell anemia in this instance, however, is based upon clear-cut clinical and anatomical findings. The history of repeated bouts of pain, both abdominal and muscular, with vomiting and "darkening of the skin," is typical. These were associated with a normocytic anemia, leukocytosis, mild icterus, large numbers of nucleated red blood cells, and a normal bleeding and clotting time. The sickling phenomenon was so prominent as to be manifest even in routine blood smears on several occasions. The anatomical changes in the spleen were precisely those described by Diggs.[5] The finding of large numbers of sickle cells in the sections further corroborates the diagnosis.

There are certain respects, however, in which this case differs from previously described cases of sickle cell anemia. The clinical history suggests that the terminal attack began in the same manner as the previous ones. On the third day, however, the patient developed chills and fever, became comatose, and presented numerous petechiae over the skin and in the conjunctivae. The petechiae faded and no new ones appeared but the patient remained comatose. It was on the third day, no doubt, that the blood was "showered" with fat emboli. The signs and symptoms a few hours before death suggest a second "shower" of emboli. The clinical picture is explained thereby and the postmortem findings are compatible with this interpretation.

The source of these fat emboli is not entirely clear. The bone marrow was necrotic, as has been previously described in cases of sickle cell anemia,[6,7] and it seems probable that this was the source of the emboli. In recorded instances of fat embolism, necrotic purulent foci and septic processes of the bone marrow have been described as the source of fat emboli by some of the early observers.[8] Lehman and Moore,[9] on the basis of *in vitro*

experiments, concluded that fat embolism might be produced readily in the bone marrow on a nontraumatic basis purely by the absorption of histamine from injured tissue into the blood stream.

The central nervous system involvement in this case is of particular interest. Several observers have previously described central nervous system lesions. Indeed, Bridgers [10] has pointed out that signs and symptoms of cerebral vascular thrombosis or intracranial hemorrhage may be the first manifestations of sickle cell anemia. Sensory and motor disturbances, headaches, nausea and vomiting, and signs of meningeal irritation are frequently reported.[11] The lesions of the nervous system have been inadequately described in most instances. Bridgers [10] described obliterative vascular lesions in one case. In another he reported the finding of multiple focal areas of necrosis and hemorrhage, apparently similar to those described in our case. The clinical picture in the two cases is also very similar.

The possible rôle of trauma or some toxic agent has been studied carefully. No evidences that either factor was involved could be obtained from careful questioning of the patient's family, or from the necropsy findings. Inasmuch as the clinical picture was fully developed prior to the patient's admission to the hospital, and in view of the glial proliferation found in the central nervous lesions, it is improbable that any manipulations such as venepunctures or subcutaneous injections following admission to the hospital played any important rôle in producing the lesions described. The similarity of the complaints and of the laboratory findings on each of the several admissions makes it improbable that toxic damage to the bone marrow by some extraneous substance need be considered.

Summary

A case of sickle cell anemia in a Greek housewife, 49 years old, is described. The known clinical history of acute exacerbations is of 6 years' duration. The terminal episode is characterized chiefly by cerebral manifestations which are adequately explained by the presence of widespread focal areas of hemorrhage and necrosis in the nervous system. These result from fat emboli which we believe to be secondary to necrosis of the bone marrow.

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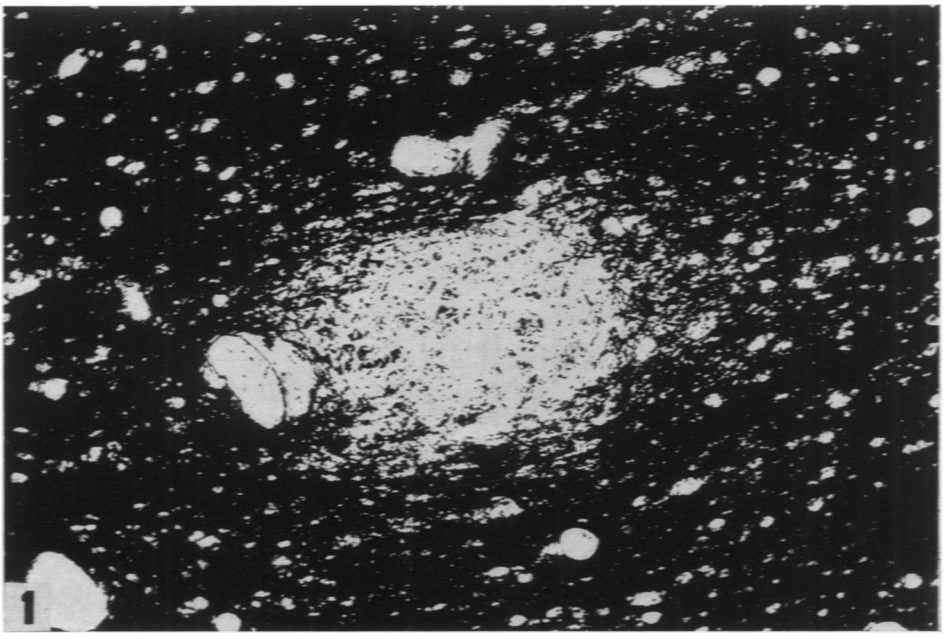
DESCRIPTION OF PLATES

PLATE 10

FIG. 1. Section of cerebral cortex (Loyez' stain for myelin sheaths) showing focal necrosis of the white matter. × 190.

FIG. 2. Hemorrhage near wall of the third ventricle (Loyez' stain for myelin sheaths) showing sickle cells. × 1500.



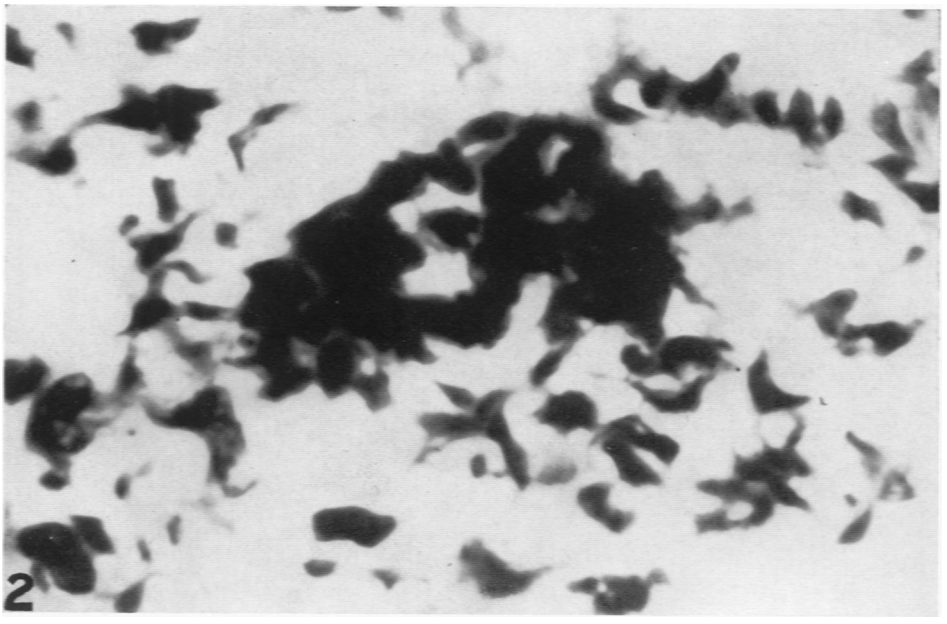


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PLATE 11

FIG. 3. Section of superior frontal gyrus of brain (Marchi's stain) showing fat emboli in capillaries surrounded by area of necrosis. × 360.

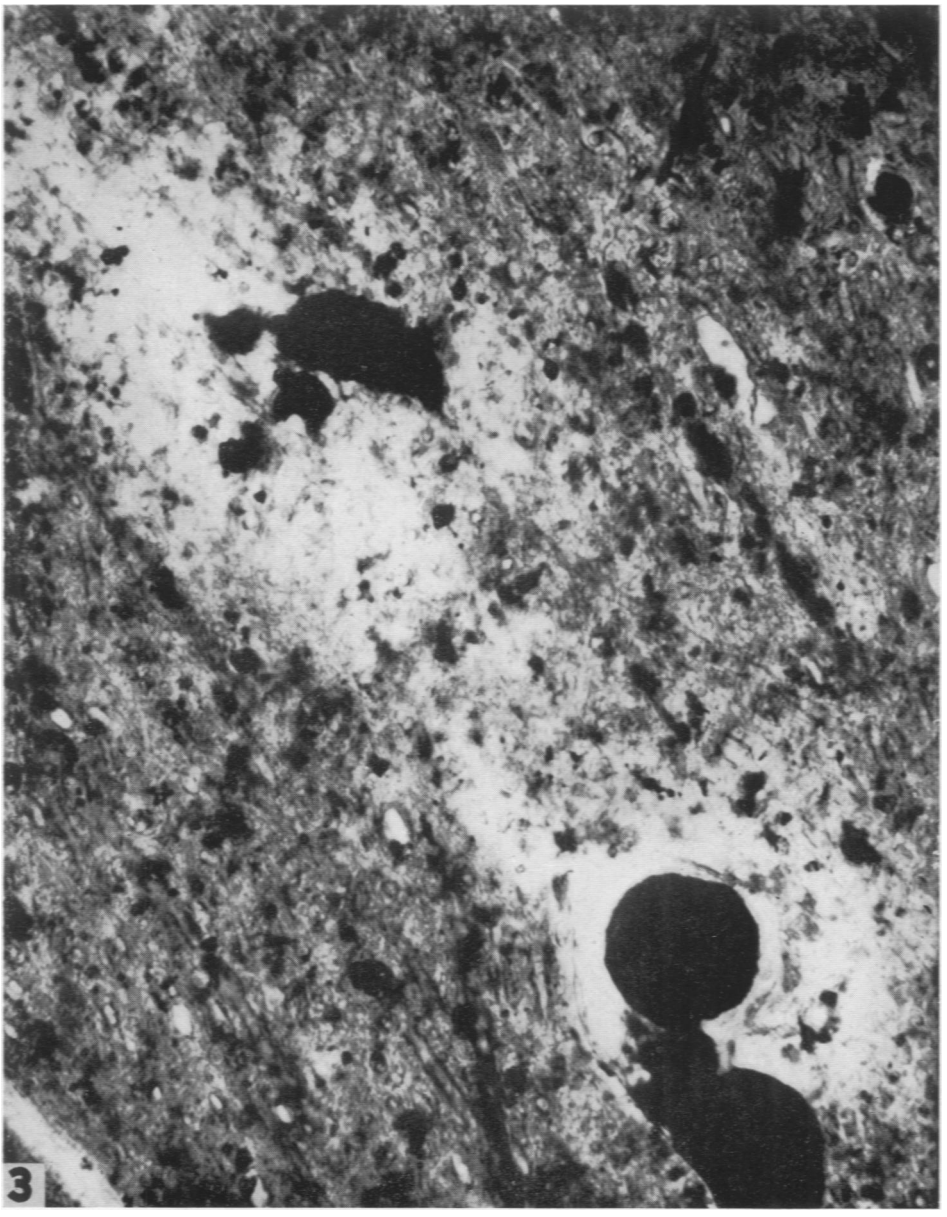

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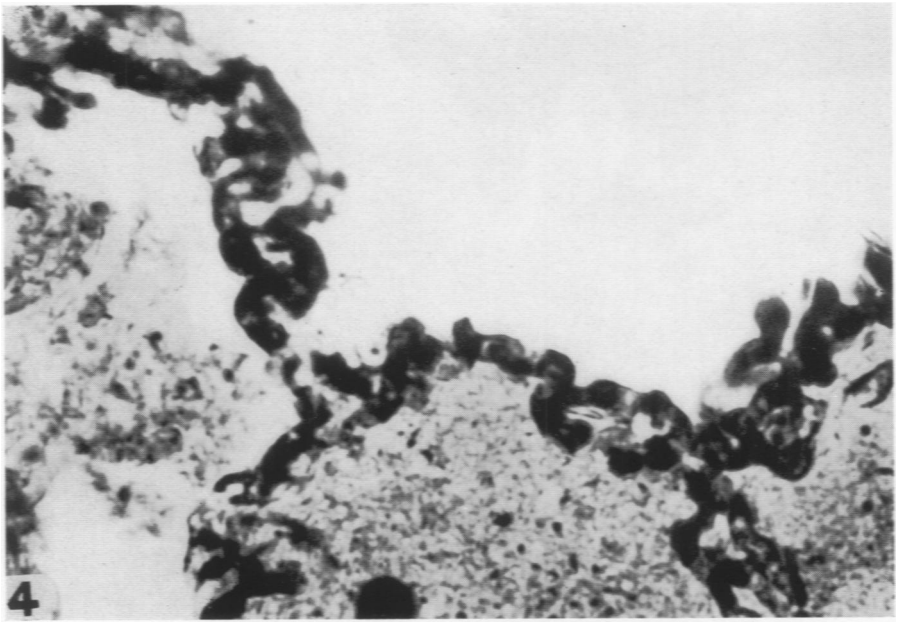
PLATE 12

FIG. 4. Section of lung (Sudan III stain) showing fat emboli in the capillaries. × 650.

FIG. 5. Section of kidney (osmic acid stain) showing fat emboli in the glomerular capillary loops. × 650.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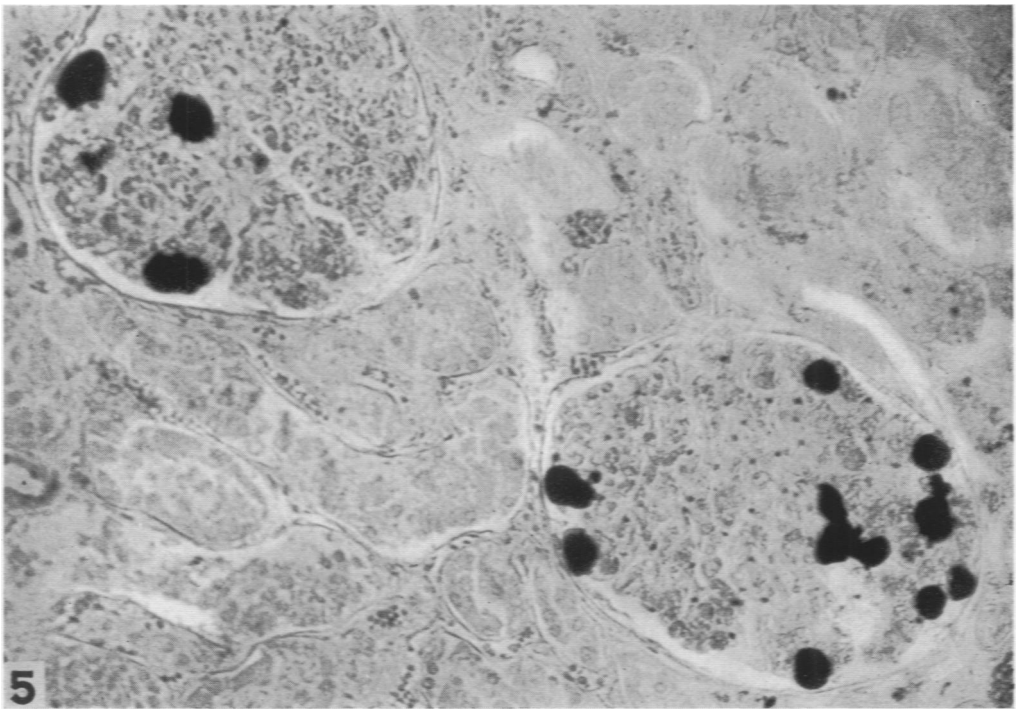
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